

Clinical Policy: Homocysteine Testing

Reference Number: CP.MP.121

Date of Last Revision: 03/25

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Description

Homocysteine is a nonproteinogenic amino acid generated during the conversion of methionine to cysteine.² Mutations of the enzymes within the biochemical pathways that regulate homeostatic homocysteine levels are associated with risk factors for various diseases such as venous thromboembolic disease.^{18,19} Supplementation of folic acid, vitamin B6, and vitamin B12 are known to modulate homocysteine levels due to the interplay between the folate cycle and metabolism.⁷ This policy describes the medical necessity requirements for testing levels of homocysteine.

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that homocysteine testing is **medically necessary** for members/enrollees with suspected homocystinuria caused by cystathionine beta-synthase deficiency including one of the following:
 - A. First-degree relative with homocystinuria;
 - B. Markedly elevated serum and urine homocysteine;
 - C. Characteristic physical findings including one of the following:
 1. Developmental delay;
 2. Marfanoid appearance;
 3. Osteoporosis;
 4. Ocular abnormalities (ectopia lentis);
 5. Thromboembolic disease;
 6. Severe premature atherosclerosis.
- II. It is the policy of health plans affiliated with Centene Corporation that homocysteine testing has not been proven to improve outcomes compared to other technologies for the following indications:
 - A. Cardiovascular risk testing;
 - B. Borderline vitamin B12 deficiency;
 - C. Dementia;
 - D. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site;
 - E. For the testing of all other conditions.

Background

Homocysteine is a naturally occurring intermediary amino acid generated during the conversion of methionine to cysteine.² Homocystinuria is a rare inherited condition where the body cannot produce methionine and is characterized by severe elevations in plasma and urine homocysteine concentrations.⁷ While homeostatic plasma levels of homocysteine typically range at low micro molar concentrations, epistatic mutations and other aberrant modifications of the metabolic pathways modulate homocysteine levels.¹ The metabolic pathway of homocysteine consists of

upstream remethylation pathways and a downstream transsulfuration pathway. Mutations in cystathionine- β -synthase, a key enzyme of the transsulfuration pathway, are associated with excess levels of homocysteine and premature thrombotic events.¹ Additionally, homeostatic levels of homocysteine are impacted by a common mutation at nucleotide position 677 of the gene coding for 5,10-methylenetetrahydrofolate reductase, which is an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine.² This mutation predisposes the individual to low folate plasma levels and consequently, a status of hyperhomocysteine.²

Changes in the plasma homocysteine levels can result from alterations in vitamin B6, vitamin B12, or folate.⁷ A meta-analysis of 25 randomized clinical trials demonstrated that daily supplementation of ≥ 0.8 mg folic acid is sufficient to achieve the maximal reduction in plasma homocysteine levels.⁸ Basal levels of homocysteine range between 5 to 15 $\mu\text{mol/L}$, while moderate hyperhomocysteine concentrations are 15 to 30 $\mu\text{mol/L}$, intermediate levels are 30 to 100 $\mu\text{mol/L}$, and hyperhomocysteine concentrations >100 $\mu\text{mol/L}$ are considered severe.⁷

Observational studies have suggested that elevated homocysteine is an independent risk factor for ischemic heart disease and vascular disease.^{3,4,15} However, large randomized controlled studies have shown that reduction in homocysteine levels does not result in lower reports of stroke or myocardial infarction.²¹ A 2017 Cochrane review of homocysteine-lowering interventions for preventing cardiovascular events concluded that B-vitamin supplements lowered homocysteine but did not reduce the risk of myocardial infarction or reduce death rates in patients with or at risk of cardiovascular disease.¹¹ Additionally, two randomized controlled trials in 2006 simultaneously demonstrated no effect on cardiovascular outcomes from lowering homocysteine levels with folic acid or vitamin B6 supplementation.^{5,6} Compared with placebo, lowered homocysteine resulting from B-vitamin supplementation combined with antihypertensive medications produced uncertain benefits in preventing stroke.¹¹

Hyperhomocysteine has also been suggested as a risk factor for venous thromboembolic disease.^{15,16,18,19} Ray et al. performed a meta-analysis of 9 case control studies measuring fasting plasma homocysteine, as well as 5 studies measured after methionine loading. All 9 studies demonstrated a similar trend in the levels and the increased associated risk for venous thromboembolism (VTE) following methionine loading.^{9,10} However, hyperhomocysteinemia has been associated with venous thromboembolic disease in some but not all studies. Additional research has concluded that associations between mild hyperhomocysteinemia and VTE may have been due to failure to consider additional confounding risk factors such as body mass index and cigarette smoking.¹⁷

Homocysteine testing has also been used to diagnose vitamin B12 deficiency in combination with methylmalonic acid (MMA). Homocysteine levels are a sensitive and specific measure of established vitamin B12 deficiency, but its role is unclear in the evaluation of borderline B12 deficiency, where it would be most useful.²⁰ Furthermore, MMA testing without concurrent homocysteine testing has been recommended in the assessment of low-normal vitamin B12 levels.²¹

High levels of serum homocysteine have been proposed as a risk factor for dementia, and several studies have evaluated the role of B-vitamin supplementation in lowering homocysteine and thus improving cognitive function or preventing cognitive decline. A meta-analysis by Clarke et al. determined that B-vitamin supplementation significantly reduced homocysteine levels, but did not have a clinically significant effect on global cognitive function or on cognitive aging.¹² In contrast, a 2018 International Consensus Statement argues for the presence of a causal relationship between homocysteine levels and cognitive decline and for screening for hyperhomocysteine and treatment with B vitamins in patients presenting to memory clinics.¹³ However, the consensus body notes that 76% of the participants in the trials in the largest meta-analysis on the topic did not include baseline measures of cognitive function, and thus could not adequately compare the intervention group to the placebo group. Furthermore, they point to the lack of an established homocysteine threshold for intervention, which reduces the clinical relevance of the measure.¹³ At this time there is a lack of conclusive evidence that vitamin supplementation prevents dementia.¹⁴

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| CPT® Codes | Description |
|-----------------------|--------------------|
| 83090 | Homocysteine |

Not Medically Necessary ICD-10 Codes

The following is a list of ICD-10 codes which are NOT medically necessary unless an exception is noted in this policy.

| ICD-10-CM Code | Description |
|---------------------------|--|
| F01.511 | Vascular dementia, unspecified severity, with agitation |
| F01.518 | Vascular dementia, unspecified severity, with other behavioral disturbance |
| F01.52 | Vascular dementia, unspecified severity, with psychotic disturbance |
| F01.53 | Vascular dementia, unspecified severity, with mood disturbance |
| F01.54 | Vascular dementia, unspecified severity, with anxiety |
| F01.A4 | Vascular dementia, mild, with anxiety |
| F01.B4 | Vascular dementia, moderate, with anxiety |
| F01.C4 | Vascular dementia, severe, with anxiety |
| F03.9 | Unspecified dementia, unspecified severity |
| F03.A4 | Vascular dementia, mild, with anxiety |
| F03.A11 | Unspecified dementia, mild, with agitation |

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| ICD-10-CM Code | Description |
|----------------|---|
| F03.B11 | Unspecified dementia, moderate, with agitation |
| F03.B4 | Vascular dementia, moderate, with anxiety |
| F03.C11 | Unspecified dementia, severe, with agitation |
| F03.C4 | Unspecified dementia, severe, with anxiety |
| G30.0 | Alzheimer's disease with early onset |
| G30.1 | Alzheimer's disease with late onset |
| G30.8 | Other Alzheimer's disease |
| G30.9 | Alzheimer's disease, unspecified |
| G31.0 | Frontotemporal dementia |
| R41.81 | Age-related cognitive decline |
| Z00.00 | Encounter for general adult medical examination without abnormal findings |
| Z00.01 | Encounter for general adult medical examination with abnormal findings |
| Z01.810 | Encounter for preprocedural cardiovascular examination |
| Z01.811 | Encounter for preprocedural respiratory examination |
| Z01.812 | Encounter for preprocedural laboratory examination |
| Z01.818 | Encounter for other preprocedural examination |
| Z13.6 | Encounter for screening for cardiovascular disorders |
| Z13.21 | Encounter for screening for nutritional disorder |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|---|-------|---------------|
| Policy developed | 07/16 | 08/16 |
| References reviewed and updated. Revised I.A from “Borderline vitamin B12 deficiency” to “Borderline low or inconclusive Vitamin B12 deficiency, or discordant with the clinical picture.” | 03/20 | 04/20 |
| Changed borderline B12 deficiency and idiopathic VTE/thromboembolism indications from medically necessary to investigational. Added supporting background information and references. Removed from the list of ICD-10 codes supporting coverage criteria: D51.0 through D51.9, E53.8, I26.01 through I26.99, I81, I82.0 through I82.91, Z86.711, Z86.718. | 05/20 | 05/20 |
| In the policy statement in section II, replaced “investigational” with the statement that homocysteine testing has not been proven to improve outcomes compared to other technologies. References and coding reviewed and updated. Replaced all instances of “member” with “member/enrollee.” | 04/21 | 05/21 |
| Annual review. References reviewed and updated. Updated description and background with no impact on criteria. Reviewed by specialist. | 03/22 | 03/22 |
| Annual review. References reviewed and updated. | 03/23 | 03/23 |
| Annual review. Expanded criteria to include I.a. First-degree relative with homocystinuria; I.b. Markedly elevated serum and urine homocysteine; I.c. Characteristic physical findings including one of the following: I.c.i. Developmental delay; I.c.ii. Marfanoid appearance; I.c.iii. Osteoporosis; I.c.iv. Ocular abnormalities (ectopia lentis); I.c.v. Thromboembolic disease; | 03/24 | 03/24 |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|--|-------|---------------|
| I.c.vi. Severe premature atherosclerosis. Added dementia as a not medically necessary indication. Updated background with no impact to criteria. Removed table of Medically Necessary ICD10 codes and replaced with a table of Not Medically Necessary ICD-10 codes. References reviewed and updated. Reviewed by external specialist. | | |
| In ICD-10 coding table, removed Z01.8 and replaced with Z01.810, Z01.811, Z01.812, and Z01.819. | 10/24 | 10/24 |
| Annual review. Background updated. References reviewed and updated. | 03/25 | 03/25 |

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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